Onartuzumab for metastatic Met positive non-small cell lung cancer

SUMMARY

Onartuzumab is a first-in-class monoclonal monovalent antibody designed to inhibit Met signalling in cancer cells by binding to the extracellular domain of Met – thereby blocking hepatocyte growth factor (HGF)-mediated activation. Overexpression of the Met receptor is associated with poor survival and resistance to erlotinib in non-small cell lung cancer (NSCLC). Onartuzumab is intended as second line treatment of stage III or IV Met-positive NSCLC. It is administered by intravenous (IV) infusion at 15mg/Kg once every 3 weeks in combination with erlotinib 150mg oral once daily until disease progression.

NSCLC is the most common type of lung cancer accounting for approximately 85-90% of lung cancers in the UK. NSCLCs are further differentiated into three main histological subgroups: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

In stage IIIB NSCLC, the tumour may be any size and has spread to lymph nodes above the clavicle or in the opposite side of the chest from the tumour; and/or to any of the organs in the thoracic cavity. Stage IV NSCLC may have spread to lymph nodes and has spread to another lobe of the lungs or to other parts of the body, such as the brain, liver, adrenal glands, kidneys, or bone.

The company estimate that around half of all advanced NSCLC tumours overexpress Met, which is associated with a poor outcome in many cancers, including NSCLC. In England and Wales, approximately 78% of newly diagnosed NSCLC patients have advanced (stage III or IV) disease that is incurable at outset. Lung cancer is the second most common cancer in the UK with around 42,000 new diagnoses in 2010, and 34,900 deaths.

Onartuzumab in combination with erlotinib is currently undergoing a phase III clinical trial assessing its effect on overall survival compared with erlotinib treatment alone.
TARGET GROUP

- Non-small cell lung cancer (NSCLC); Met-positive; relapsed stage IIIB or IV metastatic – second line after failure of prior chemotherapy; in combination with erlotinib.

TECHNOLOGY

DESCRIPTION

Onartuzumab (hOA-5D5.v2; MetMAb; OA 5D5; PRO143966; RG 3638; RO 5490258) is a first-in-class monoclonal monovalent antibody designed to inhibit Met signalling in cancer cells by binding to the extracellular domain of Met – thereby blocking hepatocyte growth factor (HGF)-mediated activation. Overexpression of the Met receptor is associated with poor survival and resistance to erlotinib in NSCLC. Onartuzumab is intended as second line treatment of stage III or IV Met-positive NSCLC. It is administered by intravenous (IV) infusion at 15mg/Kg once every 3 weeks in combination with erlotinib 150mg oral once daily until disease progression.

Onartuzumab is also currently in late stage development for the following indications:

Phase III
- Gastroesophageal cancer; metastatic; HER2 negative; Met positive
- NSCLC; EFGFR positive – first line; in combination with erlotinib (planned)

Phase II
- NSCLC; non-squamous – first line
- NSCLC; squamous – first line
- Breast cancer; metastatic; triple negative – first/second line
- Colorectal cancer; metastatic – first line
- Glioblastoma multiforme; recurrent
- Hepatocellular carcinoma; advanced (planned)

COMPANION DIAGNOSTIC

Roche is working with its subsidiary – Ventana Medical Systems – to develop and commercialise a companion diagnostic assay used to determine c-MET expression in NSCLC tumours. This assay will be used to select patients for the pivotal phase III study and the company plan to launch the validated companion diagnostic in concurrence with onartuzumab.

INNOVATION and/or ADVANTAGES

The company claim that onartuzumab utilises a novel target for its action and if licensed, may be used as an adjunct to existing treatment options in order to improve their efficacy in this patient group.

DEVELOPER

Roche Products Ltd.
**AVAILABILITY, LAUNCH OR MARKETING**

Currently in phase III clinical trials.

**BACKGROUND**

NSCLC is the most common type of lung cancer accounting for approximately 85-90% of lung cancers in the UK. NSCLCs are further differentiated into three main histological subgroups:

- Squamous cell carcinoma (33%) – this is the most common type of lung cancer. It develops in the respiratory epithelium and is often caused by smoking.
- Adenocarcinoma (25%) – develops from the cells that produce mucus in the lining of the airways (goblet cells).
- Large cell carcinoma (4%).

In addition, approximately 36% of patients are listed as being NSCLC ‘not otherwise specified’ (NOS), 1% as carcinoma in situ and 1% as bronchioloalveolar. The relative proportions of these subgroups vary over time, by population and by stage of disease. The different types of NSCLC are grouped together because they behave in a similar way and respond to treatment in a different way to small cell lung cancer (SCLC). It is often difficult to distinguish the type of NSCLC if only a few cells are taken during a biopsy or the cells are undifferentiated (called undifferentiated NSCLC). However, the histological confirmation rate is estimated to be approximately 75%. In stage IIIB NSCLC, the tumour may be any size, but it will have spread to lymph nodes above the clavicle or in the opposite side of the chest from the tumour, and/or to any of the organs in the thoracic cavity. Stage IV NSCLC has spread to lymph nodes and another lobe of the lungs, or to other parts of the body (metastases), such as the brain, liver, adrenal glands, kidneys, or bone.

The symptoms of lung cancer may include: a continuing cough, or change in a long-standing cough, dyspnoea and wheeze, haemoptysis, chest or shoulder pain, weight loss, a persistent chest infection, a hoarse voice, a dull ache or sharp pain on coughing/taking a deep breath, difficulty swallowing, fatigue and lethargy, finger clubbing, and swelling of lymph nodes in the neck area.

The company estimate that around half of all advanced NSCLC tumours overexpress Met. Upon initial diagnosis of NSCLC, Met gene amplification is uncommon; however, acquired Met amplification has been noted in up to 20% of epidermal growth factor receptor (EGFR) mutated tumours that have been pre-treated with an EGFR tyrosine kinase inhibitor (TKI) such as erlotinib. Met activation is associated with a poor outcome in many cancers, including NSCLC, and is a mechanism of resistance to EGFR inhibition.

Smoking is the main cause of lung cancer, responsible for 80% of cases. There are several other known risk factors including exposure to asbestos, arsenic, radon, and non-tobacco-related polycyclic aromatic hydrocarbons.

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a Expert clinical opinion.
This topic is relevant to: Improving Outcomes: A Strategy for Cancer (2011).

Lung cancer is the second most common cancer in the UK with around 42,000 new diagnoses in 2010, and 34,900 deaths. According to the National Lung Cancer Audit 2010 (an audit of data from hospital trusts and/or hospital sites within England that treat patients with lung cancer, amalgamated with data from other parts of the UK to produce a report on the national standards of care in England and Wales), there were 26,731 cases of NSCLC in England and Wales. Of these, 14,629 patients had stage IIIB or IV disease. In England and Wales during 2010 approximately 4,200 patients with advanced NSCLC received chemotherapy and around 30-40% of these patients receive second-line therapy. In 2011-12, there were 85,009 hospital admissions for lung cancer, of which approximately 74,400 are thought to be due to NSCLC. For patients presenting with NSCLC stage IIIB, the 5-year survival rate is around 7 to 9% whilst for patients presenting with NSCLC stage IV, the 5-year survival rate varies from 2 to 13%.

NICE Guidance

EXISTING COMPARATORS and TREATMENTS

Treatment of relapsed or metastatic NSCLC after failure of prior chemotherapy aims to improve disease control, improve quality of life and increase survival. Current second line treatment options include:

- Docetaxel monotherapy – when cancer has relapsed after previous chemotherapy.
- Erlotinib monotherapy – is recommended as an alternative to docetaxel for patients who have already progressed despite chemotherapy regimen.
- Pemetrexed – for a non-squamous histology only (not recommended by NICE for the treatment of locally advanced or metastatic NSCLC in people who have had prior chemotherapy).
- EGFR TKI (e.g. erlotinib or gefitinib) – patients with a tumour bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as second-line therapy, if not received previously (gefitinib is not recommended by NICE).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>MetLung, NCT01456325; onartuzumab vs placebo; phase III.</th>
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<tr>
<td>Sponsor</td>
<td>Roche.</td>
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<td>Status</td>
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<tr>
<td>Source of information</td>
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<td>Location</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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Participants

n=490 (planned); aged ≥18 years; incurable stage IIIb/IV NSCLC; Met-positive; ECOG performance status 0-1; prior treatment with ≥1 platinum based line of treatment; no more than 1 additional line of chemotherapy; last dose administered ≥21 days prior to day 1; tissue sample available for diagnostic testing; not exposed to an EFGR inhibitor ≥30 days.

Schedule

Randomised to onartuzumab 15mg/kg IV once every 3 weeks with erlotinib 150mg oral once daily until disease progression; or placebo IV once every 3 weeks with erlotinib 150mg oral once daily until disease progression.

Follow-up

Active treatment until disease progression.

Primary outcome/s

Overall survival.

Secondary outcome/s

Progression-free survival; overall response rate; safety. Quality of life measurement included but not specified by company.

Expected reporting date

Estimated study completion date December 2015.

ESTIMATED COST and IMPACT

COST

The cost of onartuzumab is not yet known. The cost of testing for Met expression will also have to be considered as part of the overall cost of onartuzumab. The cost of a 150mg 30 tablet pack of erlotinib is £1631.53.

IMPACT - SPECULATIVE

Impact on Patients and Carers

☑ Reduced mortality/increased length of survival
☐ Other:
☐ Reduced symptoms or disability
☐ No impact identified

Impact on Services

☑ Increased use of existing services
☐ Other:
☐ Decreased use of existing services
☐ Re-organisation of existing services
☐ Need for new services: requirement for biopsy and Met testing.
☐ Other:
☐ None identified

Impact on Costs

☑ Increased drug treatment costs
☐ Other increase in costs: additional costs for IV administration in clinic and additional costs associated with Met testing (including biopsy) and the possible requirement for re-testing.
☐ Other:
☐ Reduced drug treatment costs
☐ Other reduction in costs:
☐ None identified

ECOG (Eastern Cooperative Oncology Group) performance status: a 6 point performance scale used by clinicians to assess disease progression.

Expert clinical opinion.
Other Issues

- Clinical uncertainty or other research question
  - None identified

REFERENCES

4. Liverpool Reviews and Implementation Group. Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175. University of Liverpool; March 2013.